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Relationship between the use of an intrauterine device and ASC-US

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ABSTRACT

Aims: Cervical cancer is one of the most common gynecological cancers and has poor outcomes. Although it is more easily detected through cervical cancer screening programs, studies on the interpretation of precancerous lesions and their future consequences are among the controversial issues in literature. Atypical squamous cells of undetermined significance (ASC-US) is a category of cervical epithelial cell abnormalities described by the Bethesda system for reporting cervical cytology. It refers to abnormal cytologic changes that suggest the squamous intraepithelial lesion (SIL) but are qualitatively and quantitatively less than those of a definitive SIL diagnosis. Only some studies about intrauterine devices (IUDs), a frequently used family planning method, and causality with ASC-US have been found in the literature. Although it is known that ASC-US may be caused by inflammation, it is not clear whether an IUD can cause it. Our study aimed to evaluate the prevalence of ASC-US in women who used or did not use IUDs and to determine the risk factors associated with IUD use.

Methods: Pregnant and lactating women, women with malignancies, hormonal intrauterine devices, vaginal infections, and patients whose cervical screening data were unavailable or diagnosis of inflammation were excluded. Cervical cancer screening results of ASC-US and normal cytologic results were included in the study.

Results: At our gynecological oncology reference center, cervical cancer screening (smear + human papillomavirus [HPV]) was performed on 6452 patients between 2021 and 2022, and the smear result was interpreted as ASC-US in 306 (4.7%) of these patients. In patients without IUDs, the percentage of patients with negative ASC-US cytology was significantly greater (p:0.002) than that in patients with IUDs. The odds ratio was 1.75, as IUD-positive patients had a 1.75-fold risk of having positive ASC-US results.

Conclusion: IUDs cause inflammation, which results in ASC-US. In addition to preventing ASC-US formation, this risk can be reduced by 1.75 times by not using an IUD. Even if an IUD is used, the results of colposcopic examinations do not extend beyond the findings of inflammation.

Keywords: Atypical squamous cells of undetermined significance, colposcopy, inflammation, IUD

INTRODUCTION

Cervical cancer is the third most common gynecological cancer. The mortality and morbidity associated with cervical cancer have decreased in countries in which early diagnosis and screening are performed.

Human papillomavirus (HPV) is responsible for 99.7% of cervical pathologies and cervical cancers after eliminating non-HPV risk factors, low socioeconomic status, oral contraceptive use, smoking, and genetic predisposition. A meta-analysis in which 16 studies, including those considering nonhormonal intrauterine devices (IUDs), were evaluated revealed that cervical cancer was 30% less common in women who used IUDs (summary odds ratio [OR] 0.64, 95% confidence interval [CI] 0.53–0.77). The authors interpreted the results to indicate that cervical cancer is often less likely to be an altered immune response.[1]

IUD is one of the most commonly used family planning methods, and the device can remain in the body for a long time. Nevertheless, it is not known whether this device can cause precancerous cervical lesions. Routine smear tests are essential for detecting cervical cancer and precursor lesions, and some cervical smear results can identify abnormal cells of unknown significance (ASC-US). ASC-US results show that

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cells exhibit abnormalities that are more pronounced than simple reactive changes but not squamous lesions; in some cases, these lesions are associated with cervical intraepithelial neoplasia. Colposcopy can confirm such a result and usually reveals a low-grade intraepithelial lesion (LGSIL) or cervical intraepithelial neoplasia grade 1 (CIN1), normal cytology, and inflammation (infection). No publications in the literature addressing how an IUD (which is a foreign body) can cause inflammation and ASC-US are available.

ASC-US is an intermediate diagnosis named as a finding of abnormal cells in the tissue that lines the outer part of the cervix. ASC-US is the most common abnormal finding in a Pap test. It may be a sign of infection with certain types of human papillomavirus (HPV) or other types of infection, such as a yeast infection. It may also be a sign of inflammation, low hormone levels (in menopausal women), or a benign (not cancer) growth, such as a cyst or polyp. More testing, such as an HPV test or another Pap test, may be needed. Also called ASC-US and ASC-US.

In a review, changes of cervical cytology in IUD users was discussed and defined as cellular changes reflect reactive changes in endometrial and/or endocervical cells due to chronic irritation.[2] A study by M. Fornari[3] in 1974 was one of the early investigations that described the cellular changes associated with IUDs on cytology and was particularly notable for describing the atypical changes in glandular cells in which cytoplasmic vacuolization and some variation in nuclear size and shape could mimic adenocarcinoma. Later, a 1978 study by P. Gupta et al.[4] described cases with squamous atypia in addition to glandular atypia as well as an indeterminate type of case that included cells with high nuclear-cytoplasmic ratios, hyperchromasia, and at times, prominent nucleoli and multinucleation. They proposed at the time that these changes could be IUD-related, but that the findings were diagnostically worrisome as they could be difficult to differentiate from in situ carcinoma. In addition, in this study, IUDs are associated with two distinct cell types, vacuolated cells and small dark cells, and each pose their own diagnostic challenges given their overlap with distinct neoplastic processes.

As a result of these studies, our study aimed to define the relationship between ASC-US and IUD.

METHODS

Ethics

The study was conducted with the permission of Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRU/23.15.16). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

General Data

In our hospital, a gynecological oncology reference center, cervical cancer screening (smear+HPV cotest) was performed on 6452 patients between 2021 and 2022. The smear result was interpreted as ASCUS in 306 (4.7%) of these patients. Three hundred and six patients diagnosed with ASCUS were included in this retrospective study. Pregnant and lactating women, women with malignancies, hormonal intrauterine devices, vaginal infections, and patients whose cervical screening data were unavailable were excluded. Only cervical cancer screening results of ASC-US were included in the study.

Liquid-Based Cytological Examination

The exfoliated cells of the cervical canal and external ostium of the cervix were collected with a special brush designed for liquid-based cell tests (TCTs). The specimens were prepared with a Liqun technology centrifuge and stained with Pap. Two professional pathologists agreed on the cytological diagnosis. According to the TBS (2004) classification criteria, the TCT results were described based on specific classifications: (1) no intraepithelial lesions or malignant lesions (NILM), (2) ASC-US, (3) LGSIL, (4) atypical squamous cells without excluding high-grade intraepithelial lesions (ASC-H), and (5) high-grade squamous intraepithelial lesions (HGSIL).

HPV mRNA Detection

According to the specific steps of the Aptima HPV test kit (capture hybridization), the preservative solution of 1 ml of exfoliated cervical cells was added to the sample delivery medium (STM). Finally, the result was determined by the ratio of the signal to the threshold (s/C0). The HPV E6/E7 mRNA-positive cases were further typed and identified according to the Aptima HPV16, 18/45 genotype detection kit (capture hybridization).

This method could detect HPV 16 and HPV 18/45 E6/E7 mRNA but could not distinguish between HPV18 and HPV45. We defined HPV types as 16, 18, and others; a joint finding of ASCUS and HPV 16 or 18 will require further examination via colposcopy.

Colposcopic Evaluation

A gynecological oncologist usually performs a colposcopic examination when needed using an electronic colposcopy system (Shenzhen Jinkewei Industrial Co., Ltd.) to selectively obtain multiple biopsies in the acetic acid white and iodine test abnormally indicated areas. The biopsy tissue was fixed and preserved in 4% neutral formalin, and two professional pathologists made a diagnosis based on the routine paraffin sections.

The pathological grades included several findings:

(1) Changes in regular or chronic inflammatory responses,

(2) LGSIL;

(3) HGSIL; and

(4) Invasive carcinoma of the cervix (Ca); LGSILs and lower lesions referred to as LGSILs–, HGSILs and higher lesions referred to as HGSILs+, including HGSILs and invasive cancer.

Statistical Analysis

The data were evaluated using the SPSS 26.0 statistical program, and the percentages were calculated for the means, standard deviations, and categorical data. The normal distribution of values was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov test). Student t-tests were used to evaluate the statistical significance between two independent groups for variables with a normal distribution. The t-test was used to compare means between groups, and the chi-squared test was used for categorical data. If the values were not normally distributed, nonparametric tests were applied. For comparisons of more than two group averages, a single one-way analysis of variance (ANOVA) was used. Correlation analysis was performed for the significant means. For the level of statistical significance, $p<0.05$ was accepted.

RESULTS

Three hundred and six patients were diagnosed with ASC-US. The mean age of these patients was 43.92±10.33 (20-76) years. Less than half (45.1%) of the patients were postmenopausal. Less than one-quarter (16.3%) of patients had IUDs. Only 8% were cigarette smokers. Thirty-seven (12.1%) patients had positive human papillomavirus (HPV) tests (**Figure**, **Table 1**), and thirteen patients (4.3%) had colposcopic examination. Eleven out of thirteen patients (3.6% of total) patients were diagnosed with chronic inflammation, and two out of thirteen (0.7% of total) were diagnosed with CIN1. No statistically significant difference according to smoking status between the IUD-positive and IUD-negative groups in the ASC-US group was noted (p: 0.26).

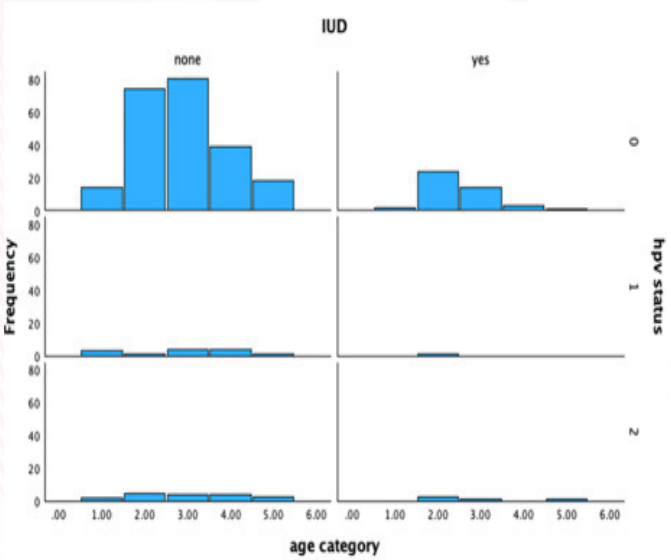

Figure. Intrauterine device and human papillomavirus (IUD and HPV, respectively) status according to age in abnormal cells of unknown significance (ASC-US) patients
Age categories: (1) ≤30, (2) 31–40, (3) 41–50, (4) 51–60, (5) >60 years
HPV status 0: none, 1: HPV16/18 positive, 2: HPV other types (non-16/18) positive

According to HPV status and categorized age, HPV positivity for 16/18 positive and other types (non-16/18) was statistically significant in ASC-US positive but IUD negative patients (p:0.04) (**Table 1, Figure**).

Out of the total 6452 cervical cancer screening patients, a group of patients with normal cytological results was chosen and divided by IUD status. This group was named the control group, ASC-US negative, normal cytological results without infection or inflammation diagnosis.

According to the Chi-Squared test results (p: 0.002), ASC-US cytology negativity was statistically significant in patients without an IUD (**Table 2**).

The odds ratio was 1.75, as IUD-positive patients had a 1.75-fold lower risk of having positive ASC-US results (p:0.018).

DISCUSSION

An IUD is one of the most commonly used family planning methods in Turkey; however, few studies addressing its relationship with HPV colonization and ASC-US are available. ASC-US is an undefined definition of squamous intraepithelial lesions. In a study by Durmus et al.[5] ASC-US prevalence was 2.1% in patients using IUDs. In our study, this percentage was 4.2%. In a study from the southeastern Turkey-Mardin region, where patients lived under similar socioeconomic conditions, the rate was reported to be 6%.[6]

In the same study[6], the rate of ASC-US was greater in the IUD-positive group than in the IUD-negative group (p = 0.02). In our study, the IUD negative group (4344/6452) had statistically significant ASC-US negative results (p:0026).

The main effect of IUDs occurs in endocervical and endometrial epithelial cells. Due to local inflammatory effects created by an IUD, edema in the endometrium, vascular congestion, necrosis, and pseudo-decidualization, especially in cells exposed to

Table 1. Distribution of different human papillomavirus (HPV) genotypes at different ages, n (%) of patients with abnormal cells of unknown significance (ASC-US) cytology

		Total number	Age				
			≤30	31–40	41–50	51–60	>60
		10	3	0	4	2	1
IUD +	HPV 16 +	0	0	0	0	0	0
IUD -		*10	3	0	4	2	1
		4	0	2	0	2	0
IUD+	HPV 18 +	1	0	1	0	0	0
IUD-		*3	0	1	0	2	0
		23	2	8	5	4	4
IUD+	Non 16/18 +	5	0	3	1	0	1
IUD-		18	2	5	4	4	3
		269	16	98	94	42	19
IUD+	HPV negative	44	2	24	14	3	1
IUD-		225	14	74	80	39	18
	Total	306	21	108	103	50	24

*Chi-square test; HPV positivity for 16/18 positive and other types (non-16/18) was statistically significant in ASC-US positive but IUD negative patients (p: 0.04), IUD: Intrauterine device

Table 2. The relationship between intrauterine device (IUD) and ASC-US cytology results

	ASC-US positive	ASC-US negative (normal cytological results and no infection/inflammation)	Total	p
IUD positive	50	512	562	
IUD negative	256	4344	4600	0.002, OR:1.75
Total	306	4856	5162	

ASC-US: Abnormal cells of unknown significance

copper IUDs, are among the observed findings.[7] These results are similar to the local inflammatory effects of ASC-US. The IUD strings consist of monofilaments and synthetic materials in contact with the cervix; such contact may trigger a chronic inflammatory response. In a study conducted with LNG and copper IUDs, inflammation was greater in these groups than in the control group without IUDs.[8] In our ASC-US positive and HPV 16/18 + group in the IUD+ group, thirteen patients had colposcopic examination. Eleven out of thirteen patients' colposcopy results were chronic inflammation.

In addition, Gupta et al.[4] reported that patients with this atypical cytology type recovered within an average of 1 to 13 months following IUD removal.

This increase in inflammation may also be due to increased infection or changes in the vaginal microbiota. In studies on this subject, Donders et al.[9] reported a greater frequency of vaginal candidiasis among LNG-IUD (IUD with levonorgestrel) users. Copper IUD is associated with bacterial vaginosis and the presence of actinomyces. Moreover, the LNG-IUD is associated with inflammatory infiltration with no specific pathogen, cytolysis, or candidiasis.[10] In our study, we exclude patients with vaginal infection and inflammation. Despite this, eleven patients had chronic inflammation result by colposcopic examination. So, this finding supported the IUD-inflammation theory.

The cytologic features of IUD cells may overlap with and thus pose diagnostic challenges concerning two main neoplastic processes: a high-grade squamous intraepithelial lesion (HGSIL) or endometrial adenocarcinoma.[11] This is only a false result because a study found that neither the LNG-IUS nor the copper IUD affects the incidence of cellular atypia.[8] In our study, no cellular atypia was found in the patients with IUD and HPV positivity in colposcopic examination.

In our study, 12.1% of patients had positive human papillomavirus (HPV) tests. It is similar with Turkey's HPV prevalence about reported between 2.0% and 46.0% in some regional studies.[12] No significant difference among IUD-positive patients according to HPV type was found ($p>0.05$). For high-risk HPV in conjunction with ASC-US findings, colposcopy was performed, but only 0.7% of patients were classified as cervical intraepithelial neoplasia grade 1 (CIN1). No patients with more advanced cervical precancerous lesions (high-grade lesions or carcinoma) were found. Our findings suggest that the cervical cytological finding of ASC-US in the presence of an IUD is more likely to indicate inflammation rather than a precancerous lesion. In a study comparing IUD and oral contraceptives (OC), the risk of CIN 3 and cervical cancer was found to be greater in the OC group.[13]

Limitations

The strengths of our study are the large population of 6452 people, the large number of patients with IUDs, the exclusion of patients with infection, and the fact that the patients were followed and accessible. The limitation of this study is that it was retrospective. However, from a result-oriented perspective, since the IUD is a contributing factor to the leading cause of inflammation, the presence of an IUD can be interpreted as such. No other studies in the literature have examined HPV, IUD, and ASC-US together.

CONCLUSION

IUDs cause inflammation, which results in ASC-US. IUD-positive patients had a 1.75 risk for ASC-US diagnosis. Even if an IUD is used, the results of colposcopic examinations do not extend beyond the findings of inflammation.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRU/23.15.16).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Castellsagué X, Díaz M, Vaccarella S, et al. Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. *Lancet Oncol*. 2011;12(11):1023-1031.
2. Risse EK, Beerthuizen RJ, Vooijs GP. Cytologic and histologic findings in women using an IUD. *Obstet Gynecol*. 1981;58(5):569-573.
3. Fornari ML. Cellular changes in the glandular epithelium of patients using IUCD--a source of cytologic error. *Acta Cytol*. 1974;18(4):341-343.
4. Gupta PK, Burroughs F, Luff RD, Frost JK, Erozan YS. Epithelial atypias associated with intrauterine contraceptive devices (IUD). *Acta Cytol*. 1978; 22(5):286-291.
5. Erdogan-Durmus S, Akalp-Ozmen S, Calik I, et al. The effects of intrauterine device on cervico-vaginal smears with liquid-based cytology technique: A North-Eastern Anatolia region study in Turkey. *Afr J Reprod Health*. 2022;26(1):47-52. doi:10.29063/ajrh2022/v26i1.5
6. Baris II, Keles AN. *[A review on the impact of IUD in cervical cytology: Mardin region data]. Turk Patoloji Derg*. 2013;29(1):51-57.
7. Buckley CH. The pathology of intra-uterine contraceptive devices. *Curr Top Pathol*. 1994;86:307-330. doi:10.1007/978-3-642-76846-0_8
8. Eleuterio J Junior, Giraldo PC, Silveira Gonçalves AK, Nunes Eleuterio RM. Liquid-based cervical cytology and microbiological analyses in women using cooper intrauterine device and levonorgestrel-releasing intrauterine system. *Eur J Obstet Gynecol Reprod Biol*. 2020;255:20-24. doi:10.1016/j.ejogrb.2020.09.051
9. Deese J, Pradhan S, Goetz H, Morrison C. Contraceptive use and the risk of sexually transmitted infection: systematic review and current perspectives. *Open Access J Contracept*. 2018;9(1):91-112.
10. Achilles SL, Austin MN, Meyn LA, Mhlanga F, Chirenje ZM, Hillier SL. Impact of contraceptive initiation on vaginal microbiota [published correction appears in *Am J Obstet Gynecol*. 2021;225(4):434.
11. Orous VF, Pitman MB. Interpretation pitfalls and malignant mimics in cervical cytology. *J Am Soc Cytopathol*. 2021;10(2):115-127. doi:10.1016/j.jasc.2020.06.005

12. Dursun P, Senger SS, Arslan H, Kuşçu E, Ayhan A. Human papillomavirus (HPV) prevalence and types among Turkish women at a gynecology outpatient unit. *BMC Infect Dis*. 2009;9(1):191.
13. Loopik DL, IntHout J, Melchers WJG, Massuger LFAG, Bekkers RLM, Siebers AG. Oral contraceptive and intrauterine device use and the risk of cervical intraepithelial neoplasia grade III or worse: a population-based study. *Eur J Cancer*. 2020;124:102-109. doi:10.1016/j.ejca.2019.10.009

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